CHRONIC TOXICITY SUMMARY

STYRENE

(ethenylbenzene, phenylethylene, vinylbenzene)

CAS Registry Number: 100-42-5

I. Chronic Toxicity Summary

Inhalation reference exposure level	**900 µg/m^3** (200 ppb)
Critical effects(s)	Neuropsychological deficits in humans as measured by memory and sensory/motor function tests
Hazard index target(s)	Nervous system

II. Chemical Property Summary

Description	Colorless to slightly yellow liquid with sweet, floral odor (HSDB, 1999)
Molecular formula	C_8H_8
Molecular weight	104.16
Boiling point	145.2 ^oC
Melting point	–31^oC (HSDB, 1999)
Vapor pressure	10 torr at 31^oC, polymerizes at 82^oC and above (Weast, 1979)
Solubility	310 µg/ml (Dean, 1985)
Conversion factor	4.26 µg/m^3 per ppb at 25^oC

III. Major Uses and Sources

The major source of styrene is industrial synthesis in which ethylbenzene is the starting material (ATSDR, 1992). The major uses of styrene are in polystyrene manufacturing, the butadiene-styrene rubber industry, and in the reinforced plastics industry (RPI) (WHO, 1983). Major non-styrene contaminants in the butadiene-styrene rubber industry are butadiene, benzene, carbon disulfide, and trichloroethylene, whereas the main co-contaminants associated with the RPI are glass fibers and acetone (WHO, 1983). Environmental exposures to styrene may result from mainstream cigarette smoke (Newhook and Caldwell, 1993) and newly installed carpets containing a styrene-butadiene rubber latex adhesive (Hodgson *et al.*, 1993). The Third National Health and Nutrition Examination Survey (NHANES) (Ashley *et al.*, 1994) reported a mean blood styrene level among ≥ 600 individuals as 0.074 ppb. In 1996, the latest year tabulated, the statewide mean outdoor monitored concentration of styrene was less than 0.1 ppb (CARB, 1999a). The annual statewide industrial emissions of styrene from facilities reporting under the Air Toxics Hot Spots Act in California based on the most recent inventory were estimated to be 2,365,873 pounds (1999b).

IV. Effects of Human Exposure

Chronic exposures to styrene (to be discussed below) result in central nervous system (CNS) and peripheral nervous system effects, although the latter are not as pronounced (ATSDR, 1992; Rebert and Hall, 1994; Murata *et al.*, 1991). Irritation or discomfort of the upper respiratory tract resulting from styrene exposure has not been reported in long-term occupational studies (Foureman, 1994). However, sensory irritation and neurological impairment does occur in acute human studies at concentrations above 100 ppm (Stewart *et*

al., 1968). The evidence for styrene induced hepatic changes is either negative or equivocal (ATSDR, 1992). Evidence for nephrotoxicity due to long-term occupational exposure is also negative or equivocal (ATSDR, 1992; Verplanke and Herber, 1998; Kolstad *et al.*,1995). Some human studies suggest that chronic exposure to styrene results in reproductive effects, but the limited data are difficult to interpret because of the small sample numbers (Brown, 1991; Lindbohm, 1993). Immunologic alterations (e.g., altered phenotypic profiles among lymphocyte subsets, decreased natural killer cell activity, and decreased chemotaxis) have also been observed, but the limited data prevent quantitative interpretation (Bergamaschi *et al.*, 1995; Governa *et al.*, 1994).

The CNS depressant effects of acute exposures to high styrene levels are probably mediated by the direct effect of the lipophilic, unmetabolized styrene on nerve cell membranes. Long-term effects of styrene exposure may result from the action of one or more metabolites of styrene (Savolainen, 1977; Mutti *et al.*, 1988). In humans, styrene metabolism is initiated by cytochrome P450 (P450)-mediated oxidation of styrene to a reactive metabolite, styrene oxide. The reaction takes place in human liver and, to a minor extent, in lung (Nakajima *et al.*, 1994). The P450 enzymes responsible for the epoxidation of styrene to stryene oxide are also found in human brain, but the brain isozymes have not been tested specifically with styrene as a substrate (Bhamre *et al.*, 1993). Styrene may also be oxidized to styrene oxide by enzymes which share specific iron and porphyrin components with P450 and those that utilize active oxygen species (Belvedere *et al.*, 1983; Tursi *et al.*, 1983; Miller *et al.*, 1992).

The major end product of styrene metabolism in humans is urinary mandelic acid (MA) and phenylglyoxylic acid (PGA) (Bardodej and Bardodejova, 1970; Leibman, 1975; Guillemin and Bauer, 1979). Other pathways that may be present in other animals are either absent or are quantitatively negligible in humans, except when high styrene levels are encountered (Guillemin and Berode, 1979; Chakrabarti *et al.*, 1993; Hallier *et al.*, 1995). Confounders of the quantitative relationship between styrene exposure and urinary MA+PGA are the consumption of ethanol (Berode *et al.*, 1986) and exposure to ethylbenzene (Bardodej and Bardodejova, 1970). An important consequence of ethanol related decreased levels of urinary mandelic acid is the potential underestimation of exposure to styrene (Guillemin and Bauer, 1979; Berode *et al.*, 1986). However, the urinary metabolite levels return to control values 4-5 hours after the ethanol consumption (Berode *et al.*, 1986).

Indicators of human styrene exposure include exhaled styrene, blood styrene, urinary MA, and urinary MA+PGA (Guillemin and Berode, 1988). Exposure to styrene by inhalation results in 89 percent absorption (Guillemin and Berode, 1988). In the occupational studies that are the basis for quantifying the relationship between chronic styrene exposure and health effects, end-of-shift or next-morning MA+PGA have been used. The next-morning measurements are more reflective of past exposures due to the high fat solubility of styrene (fat:blood partition coefficient = 94 (Csanady *et al.*, 1994)), the presence of a second, long biological half-life for MA = 25 hours., and a long biological half-life for PGA = 11 hours (Guillemin and Bauer, 1979). Following inhalation, the half-life for styrene is 41 minutes in blood (Wigaeus *et al.* 1983) and 32-46 hours in fat tissue (Perbellini *et al.*, 1988).

One postulated mechanism for the chronic non-cancer toxicity of styrene is the binding of the highly reactive styrene oxide to components of nervous tissue. Another postulated mechanism is an alteration in the levels of circulating catecholamines (e.g., dopamine) due to the binding of PGA to these biogenic amines (Mutti, 1993; Mutti *et al.*, 1984a; Checkoway, 1994) and the subsequent changes in physiological functions that are under biogenic amine control. Although long-term exposures to styrene are associated with decrements in physiological functions, the exact mechanism(s) for these effects have not been clearly established (see reviews by ATSDR, 1992; Mutti, 1993; Rebert and Hall, 1994).

Kolstad *et al.* (1995) estimated excess deaths due to four major non-malignant disease groups for 53,847 male workers in the Danish RPI. Low and high styrene exposures were based on companies with less than 50% (low) and those with 50% or more (high) employees involved with reinforced plastics. An internal comparison was made with workers unexposed to styrene to account for more similar activities and lifestyles. Statistically significant ($p < 0.05$) excess deaths due to pancreatitis and degenerative disorders of the myocardium and non-significant excess deaths due to degenerative diseases of the nervous system were observed. Non-significant excess deaths due to glomerulonephritis were also observed.

Checkoway *et al.* (1994) described a cross-sectional study of 59 male boat plant workers exposed to <1 to 144 (mean = 37.2) ppm styrene. Monoamine oxidase B (MAO-B) activity in platelets was measured as an indicator of catecholamine metabolism. When the styrene exposed workers were divided into quartile exposures, a dose dependent decrease in MAO-B activity was observed after adjustments were made for age, smoking, alcohol and medication use.

Female workers employed in the reinforced plastics industry (RPI) were studied for levels of substances associated with neuroendocrine function (Mutti *et al.*, 1984a**).** Serum prolactin, thyroid stimulating hormone, human growth hormone, follicle stimulating hormone, and luteinizing hormone were measured in 30 women who were between the 5th and 15th day of the menstrual cycle. Exposure was based on the next-morning MA+PGA, and levels of the neuroendocrine substances were measured in venous blood samples taken the next morning before the start of work. On the basis of a relationship (not detailed in the report) between urinary metabolites and styrene air concentration, the authors estimated that the average styrene TWA/8 hr was about 130 ppm. Controls consisted of women factory workers living in the same area as the styrene-exposed women, but not knowingly exposed to styrene. After controlling for age and exposure time, the increased prolactin and thyroid stimulating hormone levels were correlated with the concentration of next-morning urinary MA+PGA, although only the increased prolactin levels were statistically significant. Numerous occupational studies have noted CNS disturbances in styrene-exposed workers. Decreased manual dexterity, increased reaction times, and/or abnormal vestibuloocular reflex (ability to track moving objects) were observed by Gotell *et al.* (1972), Gamberale *et al.* (1975), Lindstrom *et al.* (1976), Mackay and Kelman (1986), Flodin *et al.* (1989), Moller *et al.* (1990), and Cherry and Gautrin (1990) for air styrene levels of about 12 ppm to more than 100 ppm. However, in each of these studies, there were difficulties in quantifying the effect. The difficulties included small sample size, unknown exposure duration, lack of concurrent control group, lack of dose-response data, and either unknown ethanol consumption or lack of adjustment for ethanol consumption. In the Cherry and Gautrin (1990) investigation, however, the authors determined that accounting for ethanol consumption did not reduce the correlation between increased reaction time and exposure.

Decrements in other CNS functions were observed among workers in the well-controlled studies of Fallas *et al.* (1992), Chia *et al.* (1994), and Mutti *et al.* (1984b). Fallas *et al.* (1992) studied 60 male workers (average age = 29.5 years, average air styrene = 24.3 ppm). The styrene-exposed population was compared to non-exposed worker controls and matched for age, intellectual level, and ethnic origin. The results from a standardized test battery showed decrements in the aiming response and 22/60 styrene exposed workers exhibited increased reaction times compared to 7/60 controls. Acquired color vision loss (dyschromatopsia) was also observed in the styrene-exposed workers compared to controls. Chia *et al.* (1994) also observed decrements in CNS function as defined by altered visual retention, audio-digit recognition, and digit recognition. However, a dose-response relationship did not exist. These workers also exhibited a statistically nonsignificant dose-dependent dyschromatopsia.

In the most comprehensive occupational study to date on CNS effects of styrene exposure, Mutti *et al.* (1984b) assessed memory and sensory/motor function in a group of 50 male styrene-exposed workers (average exposure = 8.6 years) and a control group of 50 manual workers. In addition to matching for age, sex, and educational level, a vocabulary test was included to match for general intelligence. Eligibility criteria included absence of metabolic, neurologic, or psychiatric disorders, limited ethanol intake, and limited cigarette usage. All subjects were instructed to avoid intake of alcohol and drugs for two days prior to testing. Styrene exposure was assessed from urinary MA+PGA levels the morning after the last workday in the week, followed immediately by participation in a battery of 8 neuropsychological tests designed to measure CNS function. The tests included reaction time, short and long term logic memory, short and long term verbal memory, digit-symbol association (using a reference code), block design (reproducing a displayed design using colored blocks), and embedded figures (timed identification of figures in Rey's table). The mean $\pm$ 2 SDs of the values found in the control group was set as the normal range limit for each neuropsychological test. The results were expressed as continuous and quantal data. Expressed as continuous data, styrene-exposed workers exhibited significantly poorer performances than controls in all tests, except in the digit-symbol test. Also, urinary metabolite concentration and duration of exposure were found to be significantly correlated with the scores of several tests. As a subgroup, workers with metabolite levels of up to 150 mmoles MA+PGA/mole creatinine (mean = 75 mmoles/mole creatinine $\pm$ 33 [SD], which is equivalent to a mean styrene concentration of 15 ppm) appeared to have no significant

effects. The authors state that this level of urinary metabolites corresponds to a mean daily 8-hour exposure to air styrene of 25 ppm (106 mg/m^3). Based on greater urinary excretion of styrene metabolites, significantly poorer performances in four or more neuropsychological tests were recorded in the other three subgroups (150-299, 300-450, and > 450 mmoles MA + PGA/mole creatinine).

Mutti *et al*. (1984b) expressed the quantal data as the fraction of tested subjects who responded abnormally to ≥ 1, ≥ 2, and ≥ 3 tests (see Table 1). Positive dose-response relationships existed between intensity of styrene exposure (mmoles MA + PGA/mole creatinine) and abnormal scores, whether it was expressed as abnormal responses in at least one, at least two, or at least three neuropsychological tests. The chi-square test and validity calculations were performed by constructing 2 x 2 tables selecting different levels of urinary excretion of MA and PGA as a cut-off point. The highest values for chi-square and predictive validity were found when the cut-off of 150 mmol/mol creatinine was chosen, suggesting that the quantal isolation of the low dose subgroup from the next subgroup is appropriate. When the quantal data for the low dose subgroup were analyzed by OEHHA using the Fisher's Exact Test, a significant level of abnormal responses were observed for ≥1 ($p = 0.005$) and ≥3 ($p = 0.04$) tests. The abnormal responses for ≥2 tests were statistically marginal ($p = 0.06$). For each of the remaining exposure groups, the p-values were <0.05. Unlike the assumptions made concerning the continuous data, quantal data results suggest that the low dose subgroup represents a LOAEL, and that a NOAEL is not available from the data. Mutti *et al*. (1984b) also expressed the data in a quantal three-way representation including prevalence (number of respondents for at least one, two or three abnormal tests), duration (years at work), and intensity (metabolite level). This representation revealed a positive correlation of neuropsychological deficits with duration as well as intensity.

Table 1. Subjects Classified Positive on Neuropsychological Tests as a Function of Styrene Exposure [a].

MA+PGA, mmoles per mole creatinine[b]	Total Subjects	Number of Abnormal Tests		
		≥ 1	≥ 2	≥ 3[c]
Controls	50	4/50	2/50	**0/50**
< 150 (mean = **75** ± 33)[d]	14	6/14	3/14	**2/14**
150-299 (mean = **216** ± 45)	9	6/9	5/9	**3/9**
300 - 450 (mean = **367** ± 49)	14	10/14	7/14	**5/14**
> 450 (mean = **571** ± 108)	13	11/13	8/13	**6/13**

[a] Data from Table IV in Mutti *et al.* (1984b).

[b] "Next-morning" styrene urinary metabolites.

[c] The quantal grouping of the number of subjects that performed abnormally in ≥3 tests based on their styrene urinary metabolite concentrations, both shown in bold, were used in a benchmark concentration (BMC) analysis for the derivation of the REL (see Section VI below).

[d] Based on Guillemin *et al.* (1982), a linear relationship exists for converting the urinary metabolite concentrations to ppm air styrene levels (4.97 mmoles MA+PGA/mole creatinine is equivalent to 1 ppm styrene). Thus, the mean styrene concentrations per group are 0, 15, 44, 74, and 115 ppm.In addition to dyschromatopsia observed by Chia *et al*. (1994), Gobba and Cavalleri (1993) and Campagna *et al*. (1995) also reported this visual dysfunction among styrene workers in the reinforced plastics industry. Workers (n=36) exposed to an average of 16 ppm styrene exhibited significantly greater dyschromatopsia than controls, matched for age, ethanol consumption and tobacco smoking (Gobba and Cavalleri, 1993). Among the study population, only 1/36 styrene-exposed workers (compared to 16/36 controls) performed the test with 100 percent accuracy. When a different group of styrene-exposed workers was tested, those exposed to > 50 ppm styrene exhibited greater dyschromatopsia than those exposed to ≤ 50 ppm, and within this group, a subset exhibited a similar decrement after returning from a one month vacation. In the Campagna *et al.* (1995) study, the test for dyschromatopsia was given to 81 reinforced plastics industry workers (79 male and 2 female) exposed to 4.6, 10.1, and 88.8 ppm styrene (first quartile, median, and third quartile, respectively). No control group was used in this study. Statistical analysis revealed a correlation of color vision loss with exposure to styrene (defined as next-morning urinary mandelic acid), age, and ethanol consumption.

Exposure to styrene may affect the peripheral nervous system (PNS). In a case report (Behari *et al.*, 1986), a man working for 5 years with a photostat process that used styrene was diagnosed with peripheral neuropathy. However, in occupational studies, the relationship between exposure to styrene and PNS effects has been inconsistent (Triebig *et al.*, 1985; Cherry and Gautrin, 1990). A major difficulty in understanding the potential for this relationship is the lack of knowledge about the appropriate surrogate for dose that leads to PNS disturbance (Murata *et al.*, 1991). In one study, however, chronic exposure indices were developed which included work method, years at work, time spent laminating (source of high exposure), styrene air concentration, and end-of-shift urinary mandelic acid (Matikainen *et al.* (1993). Numbness in the extremities increased with the exposure index, although statistically the effect was marginally insignificant ($p < 0.1$). The styrene TWA/8 hr was 32 ppm for the 100 study subjects.

Female reproductive toxicity has been inconsistently reported among humans (Brown, 1991; Lindbohm, 1993). These studies are difficult to interpret because of the high background rates of endpoints such as spontaneous abortion and menstrual disorders in combination with confounding exposures. In those studies that showed no reproductive effects due to styrene exposure, the power of the studies was low due to the small numbers of women. Hence the evidence for any adverse effects of exposure to styrene on female reproductive function is inconclusive.

Male workers employed in the reinforced plastics industry were examined for effects on sperm chromatin structure and semen quality (Kolstad *et al*., 1999a) and time to pregnancy (Kolstad et al., 1999b). No indications of an exposure-response relationship were seen when individual changes in semen quality were related to the postshift urinary mandelic acid concentrations among 23 exposed workers. A weak increase in sperm DNA-susceptibility to *in situ* denaturation as a function of mandelic acid concentration was indicated, but was within the interassay variability. No detrimental effect of styrene exposure was observed with regard to male fecundity among 188 exposed workers when compared to 353 unexposed workers.

Immune system alterations were reported in a study conducted by Bergamaschi *et al.* (1995). Reinforced plastics industry workers (n=32 female/39 male, average age = 32 years, average exposure duration = 7 years) were compared with non-styrene exposed factory workers and matched for age, sex, tobacco use and ethanol consumption. Air styrene levels, among the different factories, varied between 10 - 50 ppm, and individual worker exposure was measured by urinary metabolites the morning after the last shift (15 hours post-exposure). Among all workers in the study (median exposure = 16 ppm - according to the data of Guillemin *et al.* (1982)), the proportion of 12/18 lymphocyte subsets and the prevalence of abnormal values of immunologic phenotypes for 11/18 subsets were statistically different from the controls ($p < 0.001$ to < 0.05). When the workers were placed into three exposure groups (0, < 25 ppm, and > 25 ppm styrene), dose-response relationships were observed for prevalences of abnormal responses for four lymphocyte subsets and, in the case of two subsets, abnormal responses were observed in the group exposed to < 25 ppm styrene. Natural killer cell activity (a lymphocyte function), measured in a different group of workers in the same study, was decreased compared to unexposed worker controls. The median exposure, given in terms of urinary metabolites, was calculated as 21 ppm based on the data of Guillemin *et al.* (1982). The data show that exposure of these workers to air styrene levels below 50 ppm, and probably at levels near 25 ppm, resulted in alterations of the immune system.

Governa *et al.* (1994) observed reduced chemotactic responses of polymorphonuclear lymphocytes (PMNs) obtained from 21 styrene-exposed workers. However, the lack of exposure data prevents a quantitative assessment. In the same study, 0.1 - 0.6 mM styrene inhibited the chemotaxis of isolated healthy PMNs.

V. Effects of Animal Exposure

In a subchronic study, carried out under the auspices of NTP (NTP, 1992), mice and rats were exposed by inhalation to styrene vapors to establish a maximum tolerated dose for chronic studies. Mice were exposed to 0, 62.5, 125, 250, or 500 ppm styrene (6 hr/d, 5 d/wk, 13 wks). Among males deaths occurred in the 250 ppm group. Body weights among all exposed mice were lower than controls, and the difference was about 9 percent. Lung, olfactory epithelial, and forestomach lesions were observed in females and males. In females, degeneration of the adrenal gland cortex was observed. An effect not discussed in the

chairperson's report, but recorded in the original laboratory report, was an increased estrous cycle length among the female mice at all styrene doses. A LOAEL of 62.5 ppm is indicated by the olfactory epithelial, forestomach and respiratory tract lesions in mice of both sexes and for lesions in the adrenal cortex in the female mice. Rats were exposed to 0, 125, 250, 500, 1000, or 1500 ppm styrene (6 hr/d, 5 d/wk, 13 wks). No deaths occurred, but reduced body weights were observed at the two highest doses. Lesions of the respiratory tract were observed at all dose levels. A LOAEL of 125 ppm is therefore indicated for the rats.

Rats were exposed by ingestion for 2-years to styrene in drinking water (0, 125, and 250 ppm). (The water solubility of styrene is 310 ppm.) The only effect was a styrene-related reduction in water consumption (Beliles *et al.*, 1985).

Kishi *et al.* (1995) carried out a developmental study on rat pups born to dams exposed by inhalation to styrene (0, 50, 300 ppm; 6-hr/d; gestation days 7-21). Although the small number of litters (n=2) at the 50 ppm dose prevented detailed statistical analysis, the data suggest that exposure of the dams to 50 ppm styrene resulted in deficits and delays in some motor and coordination abilities among the pups. Pups born to dams exposed to 300 ppm exhibited statistically significant increases in spontaneous activity and in the delay of some neurobehavioral functions. Many of the effects became diminished as the pups aged. Measurements of reproductive toxicity (maternal weight gain, length of gestation, number of live births) did not change. Postnatal body weights were lower among the styrene-exposed pups, but the differences became less as the pups aged to 125-days.

A follow-up developmental study by the same research group investigated neurochemical levels in rat pups born to dams exposed by inhalation to styrene (0, 50, 300 ppm; 6 hr/day on gestation days 6-20) (Katakura *et al*., 1999). Cerebrum weights of day 0 pups were significantly lower when compared to cerebrum weights of *ad libitum* fed animals, but not pair-fed animals. At the highest dose, occasional reductions in neuroamines, i.e. 5-hydroxytryptamine, homovanillic acid, and 5-hydroxyindoleacetic acid, were seen in various parts of the brains of rat pups compared to one or both control groups on day 0 and day 21. No reproductive or histopathological changes were seen.

Rosengren and Haglid (1989) investigated whether long term inhalation exposure (three months) to styrene (90 and 320 ppm) could induce long lasting astroglial alterations in Sprague Dawley rats, traceable four months after exposure ceased. Styrene exposure at 320 ppm induced the alterations as shown by raised concentrations of the glial cell marker, glial fibrillary acidic protein (GFA), in the sensory motor cortex and in the hippocampus. GFA is the structural protein of the astroglial filaments. These filaments form after damage to the central nervous system from any cause. The authors concluded that exposure to styrene at moderate exposure levels induces regional, long lasting astroglial reactions that serve as an indicator of solvent induced brain damage.

Mice, exposed acutely (14 days) by inhalation to 125 - 500 ppm styrene, exhibited decreased spleen / body weight, splenic hypocellularity, altered lymphocyte proportions among subsets, and increased proliferative response to mitogens (Corsini *et al.*, 1994). Mice and rats, exposed by gavage to high levels of styrene (18, 27, 45 mg/kg - mouse; 118, 177, 294 mg/kg - rat) for 5 days/week for 4 weeks, exhibited decreased resistance to encephalomyocarditis virus, to *Plasmodium berghie* (a malaria parasite), and to *Nippostrongylus braseleinisi* (a parasitic worm) (Dogra *et al.*, 1992).

Groups of 70 male and 70 female Charles River CD (Sprague-Dawley-derived) rats were exposed whole body to styrene vapor at 0, 50, 200, 500, or 1000 ppm 6 h/day 5 days/week for 104 weeks (Cruzan *et al*., 1998). A battery of hematologic and clinical pathology examinations was conducted at 13, 26, 52, 78, and 104 weeks. Nine or 10 rats per sex per group were necropsied after 52 weeks of exposure and the remaining survivors were necropsied after 104 weeks. Control and high-exposure rats received a complete histopathologic examination, while target organs, gross lesions, and all masses were examined in the other 3 groups. Styrene had no effect on survival in males, but females exposed to 500 or 1000 ppm had a dose-related increasein survival. Levels of styrene in the blood at the end of a 6-h exposure during week 95 were proportional to exposure. Levels of styrene oxide in the blood of rats exposed to 200 ppm or greater styrene were proportional to styrene exposure concentration. The authors found no changes of toxicologic significance in hematology, clinical chemistry, urinalysis, or organ weights. Styrene-related non-neoplastic histopathologic changes were confined to the olfactory epithelium of the nasal mucosa. (The authors also found no evidence of cancer induction.)

Groups of 70 male and 70 female CD-1 mice were exposed in whole body inhalation chambers to styene vapor concentrations of 0, 20, 40, 80, and 160 ppm 6 hrs/day, 5 days/week, over a period of up to 2 years (Huntingdon Life Sciences, 1998). Ten mice per sex per group were necropsied after 52 and 78 weeks of exposure, and the remaining survivors necropsied after 104 weeks. Due to increased mortality in female control mice, terminal sacrifice for this group occurred at 98 weeks. Two female mice exposed to 160 ppm styrene died during or immediately following the first week of exposure. Histopathology revealed liver necrosis that was a likely contributor to the deaths. Reduced body weight gain and increased food consumption were observed in male mice at the two highest exposure levels and in female mice at the highest exposure level. Both styrene monomer and styrene oxide in blood increased with exposure concentration. No changes of toxicologic significance in hematology, ophthalmology, clinical chemistry, urinalysis, or organ weights were noted. Styrene-related non-neoplastic histopathologic changes were seen in the lungs (bronchiolar-alveolar hyperplasia) and nasal olfactory epithelium (respiratory metaplasia, degeneration or necrosis, and changes to the underlying Bowman's glands) from all exposure groups. The nasal lesions showed progression with time. Focal loss of bone from the turbinate was also seen more frequently as the study progressed. In addition, atrophy of the olfactory nerve fibers was present in mice at the three highest exposure concentrations.

VI. Derivation of the Chronic Reference Exposure Level (BMC Approach)

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Study	Mutti *et al.* (1984b)
Study populations	Human (occupational)
Exposure method	Inhalation
Critical effects	Central nervous system
LOAEL	15 ppm
NOAEL	Not established
BMC_{05}	1.7 ppm
Exposure continuity	8 hr/d (10 m^3 per 20 m^3 day), 5 d/wk
Exposure duration	8.6 years (average years at work)
Average occupational exposure	0.61 ppm (1.7 x 10/20 x 5/7)
Human equivalent concentration	0.61 ppm
LOAEL uncertainty factor	Not needed in the BMC approach
Subchronic uncertainty factor	1 (average exposure 12.3% of lifetime)
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	3
Cumulative uncertainty factor	3
Inhalation reference exposure level	0.2 ppm (200 ppb; 0.9 mg/m^3; 900 $\mu g/m^3$)

The most relevant chronic noncancer effect due to styrene exposure is neurotoxicity. The Mutti *et al*. (1984b) occupational study presented convincing dose-response information and was well designed and executed in terms of experimental protocol and statistical evaluation, which included tests for false positive and false negative responses. While not all confounders could be ruled out (e.g., compensatory mechanisms, biorhythms, workers who leave because of styrene related illness), careful attention was paid to include eligibility criteria for the control group that correct for confounders unique for this population (e.g., limited ethanol intake, a control work-force not exposed to neurotoxic substances, and a test to allow a match for general intelligence). The use of urinary metabolites to measure exposure dose is based on the observation that the next-morning urinary MA+PGA is directly related to the air level of styrene. The Guillemin *et al.* (1982) study provides the basis for the conversion of urinary MA+PGA levels to styrene exposure levels used by Mutti *et al.* (1984b).

The quantal dose-response data by Mutti *et al.* (1984b) is applicable for use in a benchmark concentration (BMC) approach. The quantal grouping of the number of subjects that performed abnormally in $\geq$3 tests based on their urinary metabolite concentrations was chosen for a BMC analysis (see Table 1). Basing the

BMC on abnormal responses to >3 tests reduces the complexity of multiple test comparisons and the potential for inappropriate comparison of different neuropsychological tests between control and exposure groups for statistical purposes. Also, the potential for false positive responses is reduced due to the zero background level of abnormal responses in the control group when the criteria are >3 abnormal tests. Using a log-normal probit analysis (Tox-Risk, version 3.5; ICF-Kaiser Inc., Ruston, LA) with the data (emphasized in bold typeface) in Table 1 (above) the maximum likelihood estimate (MLE) for a 5% response was 4.0 ppm. The resulting 95% lower confidence limit at the MLE provided a BMC_{05} of 1.7 ppm. A BMC_{05} is considered to be similar to a NOAEL in estimating a concentration associated with a low level of risk. Following adjustment for exposure continuity (10 m^3 per 20 m^3 day for 5 d/wk) and application of an UF of 3 to account for human intraspecies variability, a REL of 0.2 ppm (0.9 mg/m^3) was attained. For exposure data that utilizes healthy human subjects, the resulting BMC represents a less than 10% incidence in the general population. When combined with an UF of 3, as carried out above, the resulting REL will be protective of the vast majority of individuals.

This analysis of the quantal data is supported by recognizing that, in a population of 50 subjects, individual test-specific effects that occur at low doses may not have been observed. If the criterion for abnormality is expressed in terms of CNS dysfunction, defined by all tests, the sensitivity of the testing procedure is increased and the low dose effects are more easily observed. The quantal data of Mutti *et al.* (1984b), i.e., the proportion of subjects responding abnormally to the tests, therefore provide a more sensitive approach to detecting low dose effects. Collasping a battery of test data to increase sensitivity may introduce the dilemma of multiple test comparisons, as noted above. However, OEHHA believes that a statistical method to correct for this, known as a Bonferroni correction, is unnecessary. The REL development is based on calculating a statistic of one effect of a complex of responses (or a syndrome) that results from CNS dysfunction, and not based on calculating a statistic for each test within the group of tests. The apparent global nature of the neurological syndrome resulting from long-term styrene exposure, in addition to basing the BMC on abnormal responses to >3 tests, should more than adequately address any concerns that may result from combining neurological test data.

Applying NOAEL/LOAEL methodology to the Mutti *et al.* (1984b) quantal data yields an exposure value similar to that attained with the BMC approach. The LOAEL of 15 ppm is adjusted to an equivalent continuous exposure of 5.36 ppm (15 ppm x 10/20 m^3 x 5/7 d/wk). Use of a LOAEL UF of 3 and an intraspecies UF of 10 resulted in an estimated REL of 0.2 ppm (0.8 mg/m^3).

The U.S. EPA (1996) calculated a reference concentration (RfC) of 0.3 ppm (1 mg/m^3), which is slightly higher than the OEHHA-derived chronic REL of 0.2 ppm (0.9 mg/m^3). The RfC for styrene is also based on the findings of Mutti *et al.* (1984b), but utilized the continuous data for development of the RfC and used standard NOAEL methodology for the RfC derivation. U.S. EPA (1996) established a NOAEL for the lowest exposure group (<150 MA+PGA mmole/mole creatinine; equivalent to < 25 ppm styrene). However, OEHHA staff believe that the use of the continuous data to establish a NOAEL overlooks the advantages of using the BMC approach using the quantal data. These advantages are that the BMC_{05} reflects the shape of the dose-response curve and takes into account the number of subjects involved in the study. In addition, OEHHA staff evaluated the quantal data with the Fisher's Exact Test and determined the probabilities of abnormal responses among the exposed subjects based on the unexposed subjects whose responses were assumed to be normal. At the lowest exposure, the probability that the proportion of subjects responding abnormally to $\geq$1 and $\geq$3 tests was within the expected range was $p = 0.005$ and $p = 0.04$, respectively, indicating that neuropsychological deficits due to styrene occur in the low dose subgroup. Thus, the quantal data indicate that a NOAEL was not established in this study.

With regard to application of uncertainty factors, U.S. EPA (1996) applied a UF of 3 for intraspecies variability and a partial UF of 3 for lack of information on chronic studies because the critical study was considered intermediate, i.e., between subchronic and chronic duration (Foureman, 1994). OEHHA applied a UF of 1 because the mean exposure duration, 8.6 years, was greater than 12 percent of expected lifetime (8.6/70 = 12.3%). The U.S. EPA (1996) also included a modifying factor of 3 for database deficiencies. The criteria for use of modifying factors are not well specified by U.S. EPA. Such modifying factors were not used by OEHHA.

In addition to the OEHHA and the U.S. EPA hazard assessments, the Agency for Toxic Substances and Disease Registry (ATSDR) also calculated a chronic inhalation minimal risk level (MRL) for styrene (ATSDR, 1992). The calculation was based on the same Mutti *et al.* (1984b) worker study. ATSDR (1992) identified the lowest exposure group as a LOAEL and assigned an air styrene level of 25 ppm. To derive the MRL, ATSDR corrected the LOAEL for discontinuous exposure and applied uncertainty factors (UFs) for the use of a LOAEL and for intraspecies variability. The MRL was calculated as: 25 x (8/24 x 5/7) / 10 x 10 equal 0.06 ppm (ATSDR, 1992). The MRL was a factor of 3 different from the proposed REL.

For comparison, chronic exposure levels for styrene can be developed from chronic inhalation studies in rats (Cruzan *et al.*, 1998) and mice (Huntingdon Life Sciences, 1998). The mice were more sensitive to the styrene vapors than were rats, and a LOAEL of 20 ppm was identified based on lesions in various organs in both sexes. The adjustment factor for discontinuous exposure is (6/24 x 5/7) = 0.18. The uncertainty factors are: 10 for intraspecies variability, 3 for interspecies sensitivity, and 10 for adjustment from a LOAEL to a NOAEL. The resultant exposure level is (20 ppm x 0.18) / 300 which equals 0.01 ppm or 10 ppb (40 $\mu g/m^3$). Besides the different toxic endpoints between the chronic mouse exposure study and human occupational studies, the well designed human study of Mutti *et al.* (1984b) is preferable for REL development because it does not introduce the uncertainties associated with interspecies extrapolations.

The NOAEL of 50 ppm from the chronic rat study of Cruzan *et al.* (1998) may be adjusted to an equivalent continuous exposure of 8.9 ppm. Use of an RGDR of 1, an interspecies UF of 3, and an intraspecies UF of 10 resulted in an estimated REL of 300 ppb (1300 $\mu g/m^3$) for styrene.

VII. Data Strengths and Limitations for Development of the REL

The strengths of the REL for styrene include the excellent database available on styrene effects and the availability of a suitable human study for use as the key study. Limitations include the lack of direct exposure data and selection bias. Although a NOAEL was not observed in the key study, the BMC_{05} is considered to be similar to a NOAEL in estimating a concentration associated with a low level of risk.

Use of urinary metabolite concentrations to indirectly determine styrene exposure, while an accepted approach, still introduces another level of uncertainty in the hazard assessment. In addition, potential absorption of styrene via dermal exposure in the reinforced plastics industry has not been addressed and may overestimate the air concentration determined by urinary metabolite levels. However, unlike air levels, the presence of urinary metabolites of styrene gives an unequivocal indication that an individual has been exposed to styrene. At the present time, a system does not exist to obtain direct exposure information, although a recent report suggests a methodology is being developed (Jensen *et al.*, 1995).

A potential bias in the key study was the finding that general intelligence, as measured by the vocabulary test, appeared to be negatively correlated with both age and exposure intensity. This finding suggests that age may also be a factor in poor neuropsychological test scores of highly exposed subgroups. Another source of uncertainty is that the reinforced plastics industry, from which the workers in the Mutti *et al.* (1984) study were taken, is characterized by a large turnover of highly exposed workers (Wong, 1990; Kogevinas *et al.*, 1993). This possible selection bias may result in more sensitive workers leaving employment while more tolerant workers remain.

VIII. References

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